

[0016] FIG. 7 illustrates a table of values obtained from logistic regression analysis and AUC for models of CAD adjusted for age and sex, according to an embodiment of the present disclosure.

[0017] FIG. 8 illustrates scatter plots of the traditional heart rate variability (rMSSD, pNN50 and HF), nonlinear (α_1 and SampEn) and fragmentation (PIP, IALS, PSS and PAS) indices versus mean heart rate (in beats per minute, bpm) for the group of healthy subjects (blue dots) and those with coronary artery disease (CAD, red circles), derived from the analysis of 24-hour NN interval time series, according to an embodiment of the present disclosure.

[0018] FIG. 9 illustrates examples of respiratory sinus arrhythmia and anomalous (fragmented) sinus rhythm, according to an embodiment of the present disclosure. Electrocardiograms (Holter lead) from a healthy subject (first row) and a patient with coronary artery disease (CAD) (second row), both from the present study. Normal-to-normal (NN) sinus interval time series from the healthy subject (third row, left) and the patient with CAD (third row, right). The fluctuation patterns of the former time series are characteristic of phasic (respiratory) sinus arrhythmia, while that of the latter are indicative of an abnormal, non-phasic sinus arrhythmia. See Costa, M. D., Davis, R. B., and Goldberger, A. L. (2017). Heart rate fragmentation: a new approach to the analysis of cardiac interbeat interval dynamics. *Front. Physiol.* 8:255 (herein “Costa I 2017”). Positive and negative changes in the value of the NN intervals, corresponding to heart rate decelerations and accelerations were mapped to symbols “-1” and “1,” respectively. Symbol “0” is used to represent intervals in which heart rate did not change. To assist in visual comparisons, pale gray backgrounds are used for data from the healthy subject and light red for data from the patient with CAD, respectively. The symbolic mapping of the differences between consecutive NN intervals for the ECG of the healthy subject (first 16 intervals) along with the first four words that were derived from this sequence are shown on the bottom left. The first word “-1-111” contains one hard inflection point. It belongs to the group W_1 and, more specifically, to the subgroup W_1^H . The following three words, “-1110,” “110-1,” and “10-1-1” contain two inflection points. Therefore, they belong to group W_2 . However, the first word (“-1110”) belongs to the subgroup W_2^M since it contains one hard and one soft inflection point; the second (“110-1”) and the third (“10-1-1”) words belong to the subgroup W_2^S since they present two soft inflection points. The panels on the bottom right show the percentage of words in each group for the healthy subject (left) and patient with CAD (right). Note a substantially higher percentage of fragmented words for the patient with CAD than for the healthy subject. The abbreviation “a.u.” stands for arbitrary units.

[0019] FIG. 10 illustrates a schematic diagram of 81 different words of length 4 with an alphabet of 3 symbols, in which the symbols “/”, “\”, and “-” represent heart rate acceleration, deceleration and no change, respectively. Words were grouped by the number and type of inflection points. The labels, 0-80, shown in parentheses, are the decimal value of the ternary representation of each pattern using the symbols “2” if $\Delta NN_i < 0$, “1” if $\Delta NN_i > 0$ and “0” if $\Delta NN_i = 0$. For example, the label for the word comprising 4 consecutive accelerations, i.e., the word 2222, is 80 ($= 2 \times 3^3 + 2 \times 3^2 + 2 \times 3^1 + 2 \times 3^0$). Abbreviations: W , word subgroup. The subscript and superscript of W indicate, respectively, the

number and the type of inflection points, hard (H), soft (S) or a combination of hard and soft (M, mixed) that the words in that subgroup contain.

[0020] FIG. 11 illustrates a table of slope and [95% confidence intervals] of the association between each outcome measure and the participants’ age for the group of healthy subjects and those with CAD, for the 24-h and putative awake and sleep periods. CAD, coronary artery disease; PIP, percentage of inflection points; W_j , $0 \leq j \leq 3$, group of words containing j inflection points; superscripts: H, hard inflection points; S, soft inflection points; M, mixed inflection points, i.e., a combination of hard and soft inflection points. Word groups for which the type of inflection point is not specified comprise words with all types of inflection points. The percentages of words in the groups W_j^{H*} and W_j^{S*} were calculated over the total number of NN words with only hard and only soft inflection points, respectively. The percentages of words in the other groups were calculated over the total number of NN words. Slope values marked with the symbol † are significantly different in the two sample populations.

[0021] FIGS. 12A-12C illustrate graphs depicting the relationship between the percentage of words with no inflection points (W_0), one (W_1), two (W_2) and three (W_3) inflection points and the participants’ age for the healthy subjects (blue) and those with coronary artery disease (CAD, red) during the 24-h (FIG. 12A), putative awake (FIG. 12B) and putative sleep (FIG. 12C) periods. Symbols and lines represent, respectively, word percentages for each subject and the regression lines derived from linear regression analyses controlled for the average NN interval. In each plot, the rates of change of the outcome variables per year of age for the healthy subjects and the patients with CAD are indicated in blue and red, respectively.

[0022] FIG. 13 illustrates a table showing measures of heart rate fragmentation/fluency in healthy subjects and those with coronary artery disease. Values are reported as median, 25th-75th percentiles. CAD, coronary artery disease; PIP, percentage of inflection points; W_j , $0 \leq j \leq 3$, group of words containing j inflection points; superscripts: H, hard inflection points; S, soft inflection points; M, mixed inflection points, i.e., a combination of hard and soft inflection points. Word groups for which the type of inflection point is not specified comprise words with all types of inflection points. The percentages of words in the groups W_j^{H*} and W_j^{S*} were calculated over the total number of NN words with only hard and only soft inflection points, respectively. The percentages of words in the other groups were calculated over the total number of NN words.

[0023] FIG. 14 illustrates a table showing logistic regression analysis and area under the ROC curve for unadjusted models of CAD. Values presented are normalized odds ratio (OR_n), 95% confidence intervals (95% CI) and area under the receiver operating characteristic curve (AUC). CAD, coronary artery disease; PIP, percentage of inflection points; W_j , $0 \leq j \leq 3$, group of words containing j inflection points; superscripts: H, hard inflection points; S, soft inflection points; M, mixed inflection points, i.e., a combination of hard and soft inflection points. Word groups for which the type of inflection point is not specified comprise words with all types of inflection points. The percentage of word groups without “*” was calculated over the total number of NN words. The percentages of words in the groups W_j^{H*} and W_j^{S*} were calculated over the total number of NN words